Examiner contends that Markowicz et al. teaches utilization of 100 U/ml of GM-CSF and IL-4. In addition, the Examiner contends that Jakoby et al. teaches that optimization of experimental conditions for cell culture, including the adjustment of the concentration of culture medium additives, was well known in the art. Applicants traverse this ground of rejection.

The Examiner again relies primarily on Markowicz et al. to support the ground of rejection. Applicants respectfully request reconsideration of applicants' response filed on March 4, 1997 which points out that Markowicz et al. **does not** refer to proliferating dendritic cell precursors which are the subject of the pending claims. Without addressing this issue, the Examiner incorrectly presumes that Markowicz et al. is relevant to proliferating cells when in fact it states "At any given concentration of the cytokine, however, the total number of viable cells as sell as the number of branched cells per well remained stable over time suggesting that GM-CSF does not cause DC to divide and proliferate." The Examiner's statement that "Markowicz et al. differs from the claimed invention by not specifically indicating the exact concentration level of IL-4 utilized and also by teaching the utilization of a slightly less concentration level of GM-CS from that which is specifically claimed" confirms that the Examiner has not considered the full scope of the claims which also require the step of "culturing the tissue source on a substrate and in a culture medium to produce **proliferating dendritic cell precursors....**" The Examiner has

simply not provided any basis as to how Markowicz et al. would teach or suggest, or provide any motivation, to obtain proliferating dendritic cell precursors according to the method claimed by applicants.

The Examiner's further reliance on Jakoby et al. does not provide any further basis to support the ground of rejection. The portion of Jakoby et al. relied on by the Examiner generically refers to determination of "optimum" concentrations of medium components. The optimization which is referred to by Jakoby et al., however, is in the context of "systematically adjust[ing] the concentrations of all components of the medium to optimum concentration for clonal growth." Jakoby et al. at 76. This quantitative optimization does not teach or suggest that the choice of the particular components to be included in a medium to sustain proliferation is obvious. Jakoby et al. itself recognizes the complexity of cell requirements and states:

> The data are still incomplete, but it currently appears highly probable that most such cells have specific requirements for protein growth factors that **cannot easily be replaced** by improvements in the low-molecular-weight portion of the culture medium or in other aspects of the culture system....

Jakoby et al. at 46.

Thus, in view of the failure of Markowicz et al. to relate to proliferating dendritic cells, and the complexity of culture requirements as recognized even by Jakoby et al., the choice of medium components and culture conditions in the methods

claimed by applicant is not obvious. Applicants therefore respectfully request removal of this ground of rejection.

Rejection of Claims 7 and 13 Under 35 U.S.C. 103

Claims 7 and 13 stand rejected under 35 U.S.C. § 103 over Markowicz et al. in view of Koch et al. The Examiner contends that Koch et al. teaches that insight into dendritic cells may be obtained from Langerhans cells and that Koch et al. "teaches that the addition of TNF-alpha to murine epidermal Langerhans cells in culture allows such cells to maintain their viability." According to the Examiner, it would have been obvious to one skilled in the art to add TNF-alpha to the dendritic cell cultures of Markowicz et al. Applicants traverse the Examiner's rejection and respectfully request reconsideration.

As stated previously, neither Markowicz et al. nor Koch et al. teach or suggest methods of obtaining mature, functional dendritic cells from **proliferating** dendritic cell precursors. Even if Langerhans cells were predictive of dendritic cells, which applicants do not generally concede, Koch et al. refers to the activity of cytokines to maintain the survival of Langerhans cells and does not provide any teaching or suggestion concerning a method for producing mature dendritic cells from proliferating dendritic cell precursors.

The Examiner's reliance on the reference in Koch et al. to the ability of TNFalpha to maintain viability of Langerhans

cells does not make applicants' invention obvious in combination with Markowicze et al. because maintaining viability is a different response from allowing for, or stimulating, proliferation. For example, certain growth factors which enhance survival lead to an inhibition of proliferation. Thus, there is no basis to form the analogy as performed by the Examiner and applicants respectfully request removal of this ground of rejection.

Rejection of Claims 8-9 and 23 Under 35 U.S.C. § 103

Claims 8, 9 and 23 stand rejected under 35 U.S.C. § 103 as being unpatentable over Markowicz et al. and further in view of Voorhis et al. or Ruly et al. The Examiner contends that Voorhis et al. teach that human dendritic cells may be cultured in 5-10% fetal calf serum and Ruly et al. teaches using cord blood serum in cell cultures. Again, neither of these publications provide any teachings about proliferating dendritic cell precursors and applicants request removal of this ground of rejection.

Conclusion

Applicants claim a method of producing a population of mature dendritic cells from **proliferating dendritic precursors.** The claimed method requires that a tissue source comprising such precursors be cultured in medium comprising GM-CSF **and** a factor which **inhibits** the proliferation or maturation of non-dendritic

cell precursors so as to increase the proportion of the dendritic cell precursors. The claims thus require that a factor be included in the medium which inhibits proliferation of one cell type while not inhibiting the proliferation of another. None of the publications relied on by the Examiner teach or suggest anything about proliferating dendritic cell precursors. Thus, one skilled in the art could not possibly have any basis to have a reasonable expectation of successfully obtaining mature dendritic cells according to the claimed method based on the cited publications.

Applicants also bring to the Examiner's attention that co-pending U.S. application 458,230, a continuation of 040,677, the parent of this application has recently been allowed over Markowicz et al.

In view of the above, applicants request removal of the remaining rejections and issuance of a Notice of Allowance.

AUTHORIZATION

No additional fee is believed due in association with this response. However, the Commissioner is hereby authorized to charge any additional fees which may be required for this Amendment, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2016-4000US3. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

If any questions or issues remain or if the examiner has any comments or suggestions for expediting allowance of this

application, he is urged to contact the undersigned at the telephone number below.

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

Dated: October 15, 1997

By: Kenneth H. Sonnenfeld

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on October 15 1997

Kenneth H. Sonnenfeld

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